REMARKS

Reconsideration of the above-identified application in view of the amendment above and the remarks below is respectfully requested.

No claims have been canceled or added in this paper. Claim 1 has been amended in this paper. Therefore, claims 1-12, 14-18, 20-23, 25-26, 30-34, 36 and 41 are pending and are under active consideration.

Claims 1-12, 14-18, 20-23, 25-26, 30-34, 36 and 41 stand rejected under 35 U.S.C. 101 "because the claimed invention is directed to non-statutory subject matter." In support of the rejection, the Patent Office states the following:

> Claims 1-12, 14-18, 20-23, 25, 26, 30-34, and 36 are drawn to a process and claim 41 is drawn to a device that executes the process. A statutory process must include a step of a physical transformation, or produce a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). The instant claims do not result in a physical transformation, thus the Examiner must determine if the instant claims include a useful, concrete, and tangible result.
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> As noted in State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998) below, the statutory category of the claimed subject matter is not relevant to a determination of whether the claimed subject matter produces a useful, concrete, and tangible result:
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> > The question of whether a claim encompasses statutory subject matter should not focus on *which* of the four categories of subject matter a claim is directed to 9—process, machine, manufacture, or composition of matter—but rather on the essential characteristics of the subject matter, in particular, its practical utility. Section 101 specifies that statutory subject matter must also satisfy the other "conditions and requirements" of Title 35, including novelty, nonobviousness, and adequacy of disclosure and notice. See *In re Warmerdam*, 33 F.3d 1354, 1359, 31 USQP2d 1754, 1757-58 (Fed. Cir. 1994). For purposes of our analysis, as noted above, claim 1 is directed to a machine programmed with the Hub and Spoke

software and admittedly produces a "useful, concrete, and tangible result." *Alappat*, 33 F.3d at 1544, 31 USPQ2d at 1557. This renders it statutory subject matter, even if the useful result is expressed in numbers, such as price, profit, percentage, cost, or loss.

In determining if the claimed subject matter produces a useful, concrete, and tangible result, the Examiner must determine each standard individually. For a claim to be "useful" the claim must produce a result that is specific and substantial. For a claim to be "concrete" the process must have a result that is reproducible. For a claim to be "tangible" the process must produce a real world result. Furthermore, the claim must be limited only to statutory embodiments.

Claims 1-12, 14-18, 20-23, 25, 26, 30-34, 36, and 41 do not require production of a tangible result in a form that is useful to the user of the process or apparatus. The claims conclude with addition of selected genes to a gene panel. A gene panel is discussed on pages 17-18 of the specification as a knowledge base present in forms of computer readable memory including a computer disc, RAM, and ROM, or a printed table. Data in the form of signals in RAM and ROM or even a physical computer disc are not necessarily limited to tangible outputs that are in a format that is interpretable by a user of the claimed method or device. A tangible result requires that the claims must set forth a practical application to produce a real-world result. This rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical format, or in a user readable format, or by including a result that is a physical transformation. The applicants are cautioned against introduction of new matter in an amendment.

begin with an article which is required by rules of grammar, and further required to ascertain if a dependent claim requires all limitations of the claim from which it depends (when the article is "the") or if the dependent claim only requires a portion of the limitations of the claim from which it depends (when the article is "a").

Claims 1-12, 14-18, 20-23, 25, 26, 30-34, 35, and 41 recite biological samples that should be modified by an adjective in claim 1, but instead are modified by a noun "cancer" in the wherein clause. The term "cancer" should be amended to recite "cancerous."

Without acquiescing in the propriety of the rejection, Applicants have amended claim 1 to additionally recite the step of outputting the result in a user readable format. Given that the Patent Office has stated in the outstanding Office Action that "[t]his rejection could be overcome by amendment of the claims to recite that a result of the process is outputted to a display, or to a user, or in a graphical format, or in a user readable format, or by including a result that is a physical transformation," Applicants respectfully submit that the present amendment obviates the rejection.

Accordingly, the subject objection has been obviated and should be withdrawn.

Claims 1-12, 14-18, 20-23, 25-26, 30-34, 36 and 41 stand rejected under 35 U.S.C. 112, first paragraph, "as failing to comply with the written description requirement." In support of the rejection, the Patent Office states the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention.
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> The claims are drawn to a method of determining genes that have differences in expression and methylation relative to two cancerous biological samples. The specification describes a method of determining genes that have differences in expression and methylation relative to two groups of samples on page 11, relative to healthy and/or diseases samples on page 12, and relative to prostate cancer cell lines and healthy prostate cells on page 12. The specification does not describe a method of determining genes that have differences in expression and methylation relative to two cancerous samples.

Applicants respectfully traverse the subject rejection. In the paragraph bridging pages 21 and 22 of the substitute specification, the following passage appears:

> A preferred method according to the invention is characterised in that the at least one biological sample is derived from biological material of healthy and/or diseased individuals. Such diseases include all diseases and/or medical conditions which involve a modification of the expression of genes of the cell and include, for example,...cancers....

The Patent Office is apparently taking the position that the above passage does not encompass at least two cancerous samples. Applicants respectfully disagree. The passage clearly states that there is at least one biological sample and that said at least one biological sample is derived from healthy and/or diseased individuals. The Patent Office is construing this language to require that, if there are two samples, one sample is from a healthy individual and the other is from a diseased individual. Applicants respectfully submit that, although the language in question encompasses the aforementioned scenario, it is clearly not limited thereto. The language in question recites at least one sample from healthy and/or diseased individuals. As such, the language encompasses, but is not limited to, the three following possibilities: (1) two healthy samples; (2) two diseased samples; and (3) one healthy sample and one diseased sample. In order for the Patent Office's more limited interpretation to be correct, the language in question would have to read "one biological sample from a healthy individual and one biological sample from a diseased individual." This is not how the language in question reads. The fact that the language in question recites **at least one** biological sample and then recites healthy and/or diseased individuals, as opposed to healthy **and** diseased individuals, clearly expresses that the present invention contemplates deriving a plurality of samples from only diseased individuals.

Accordingly, the subject rejection should be withdrawn.

Claims 1-12, 14-18, 20-23, 25-26, 30-34, 36 and 41 stand rejected under 35 U.S.C. 112, first paragraph, "as failing to comply with the enablement requirement." In support of the rejection, the Patent Office states the following:

> The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
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> In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.
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> In considering the factors for the instant claims:
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> a) In order to practice the claimed invention one of skill in the art must make a gene panel useful for diagnostic and therapeutic purposes by comparison of the gene expression and DNA methylation levels of two cancerous samples. For the reasons discussed below there would be an unpredictable amount of experimentation required to make the claimed invention.
> b) The specification presents guidance on pages 11 and 12 to compare healthy and diseased samples when practicing the claimed method.
> c) The specification presents a working example on page 21 of comparison of prostate cancer cell line cells to healthy prostate cells when practicing the claimed invention.
> d) The nature of the invention, molecular diagnostic assays, is complex.

e) Huang et al. shows a method of determining methylation sites relevant to breast cancer. Huang et al. shows in the abstract and throughout that the comparison was done between breast cancer cells and normal tissue so that differences that correlate with breast cancer could be determined.

f) The skill of those in the art of molecular diagnostic assays is high.

g) It is predictable from prior art such as Huang et al. that qualities of cancerous samples that are relevant to disease for diagnostic or therapeutic purposes should be compared to normal tissue controls so that the changes are known to appear only in diseased tissue.

h) The claims are broad in that they require determination of gene panels useful for diagnostic or therapeutic purposes to be determined without determining whether the gene panels contain genes whose expression and methylation levels correlate with disease.

The skilled practictioner would first turn to the instant specification for guidance and working examples to practice the claimed method of making gene panels. However, the specification does not provide such guidance or working examples. Next, the skilled practitioner would turn to the prior art for such guidance. The prior art shows that genes related to disease should be assessed relative to normal tissue controls. Finally, said practitioner would turn to trial and error experimentation to make and use the claimed subject matter, which represents undue experimentation.

Applicants respectfully traverse the subject rejection. The subject rejection is predicated, in part, on the Patent Office's position that the present specification does not teach using two samples, each of which is cancerous. As explained above, Applicants respectfully submit that the Patent Office's position is in error. At no point in the specification is it stated that it is necessary that diseased biological material be compared to healthy.

In addition, Applicants respectfully submit that, although some experimentation may be needed, the amount of said experimentation would not be undue and would amount to no more than routine experimentation. This is because the only experimentation needed in the method of the invention involves performing a number of well-established, routine biochemical assays. In fact, at the time of the invention, such assays were being performed in an automated and high-throughput manner. For example, the use of DNA arrays to establish the methylation status of the genome, and gene expression were known in the art. Moreover, the working example in the present specification could easily be carried out by substituting a diseased prostate sample for the healthy. This would require no technical changes to the expression or methylation assays.

Finally, to the extent that the Patent Office's position is predicated on the notion that diseased samples must be compared to healthy samples for meaningful information to be obtained, Applicants respectfully disagree. It is not uncommon in the art for different types of diseased tissues to be compared to one another. For example, different classes of cancer of a single cancer type may be compared in order to establish markers that are useful in the treatment of diseases, by more accurately classifying the disease. An example of this would be "Methylation alterations of the MyoD1 upstream region are predictive of subclassification of human rhabdomyosarcomas." Am J Pathol. 1998 Apr;152(4):1071-9. PMID: 9546368. In addition, benign hyperproliferative disease has been compared to malignant hyperproliferative disease in order to diagnose cancers in which abnormal tissue growth is observed in a patient. An example of this would be "Global DNA hypomethylation increases progressively in cervical dysplasia and carcinoma." Cancer. 1994 Aug

1;74(3):893-9. PMID: 8039116. Consequently, the claimed method may be used to provide a gene panel which gives a clinician information, for example, about a comparison of a benign vs. malignant cancer. This would provide useful information as to whether a diagnosed proliferative disorder was cancer, as opposed to a benign hyperproliferative disorder.

In conclusion, Applicants respectfully submit (1) that the specification clearly states that diseased tissue types may be compared to other diseased tissue types, (2) that one of ordinary skill in the art would know how to perform the experiments (assays) required by the claimed method and, furthermore, that said assays are completely routine and automatable, and (3) that the art clearly shows that diseased tissue types may be compared to other diseased tissue types.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on July 14, 2008.

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Edward M. Kriegsman